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(54) Title: A PHARMACEUTICAL COMPOSITION COMPRISING ANTISENSE-NUCLEIC ACID FOR PREVENTION AND/OR TREATMENT OF NEURONAL INJURY, DEGENERATION AND CELL DEATH AND FOR THE TREATMENT OF NEOPLASMS			
(57) Abstract A pharmaceutical composition comprising an effective amount of a compound which is capable of preventing and treating neuronal injury, degeneration, cell death and/or neoplasms in which expression of <i>c-jun</i> , <i>c-fos</i> or <i>jun-B</i> plays a causal role which compound being an antisense nucleic acid or effective derivative thereof, said antisense nucleic acid hybridizing with an area of the messenger RNA (mRNA) and/or DNA encoding <i>c-jun</i> , <i>c-fos</i> or <i>jun-B</i> .			

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A pharmaceutical composition comprising antisense-nucleic acid for prevention and/or treatment of neuronal injury, degeneration and cell death and for the treatment of neoplasms

The present invention is related to a pharmaceutical composition and a diagnostic agent comprising an effective amount of a compound which is capable of preventing and treating neuronal injury, cell death and/or neoplasms in which expression of c-jun, c-fos or jun-B plays a causal role, particularly, antisense nucleic acid or -oligonucleotides hybridizing with an area of the messenger RNA (mRNA) and/or DNA comprising the genes for c-jun, c-fos or jun-B; the use of the compound for the preparation of a pharmaceutical composition for the treatment of neoplasms and/or the prevention and/or treatment of neuronal injury and degeneration related with the expression of c-jun, c-fos or jun-B.

Schlingensiepen et al. report in Proceedings of the American Association for Cancer Research, Vol. 32, p. 303, Abstract No. 1799, 82. Annual Meeting of the American Association for Cancer Research, Houston, USA, 1991 that c-jun and jun-B genes share high sequence homology with the v-jun gene. They belong to the immediate early gene group. C-jun together with c-fos constitutes the DNA binding factor AP-1. C-jun and

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jun-B expression was inhibited in different cell lines using phosphorothioate oligodeoxynucleotides. C-jun inhibition strongly reduced 3H-thymidine incorporation in two mammary carcinoma cell lines, in the rat pheochromocytoma cell line PC-12 and in NH 3T3 mouse fibroblasts. The inhibition of c-jun expression and of c-fos expression had very similar effects in the same cell lines inhibition of jun-B expression drastically increases 3H-thymidine uptake to more than 10fold. 10-jun is meant to have the characteristics of a proto-oncogene but jun-B appears to be an anti-oncogene with strong anti-proliferative action similar to that of p53. The results suggest that jun-B and c-jun to be functional antagonists with regard to their effect on cell growth. This investigation was carried out in order to elucidate the function of respective genes and proteins. This abstract does not suggest any therapeutic concept.

From the Journal of Cellular Biochemistry, Abstract B 977, Keystone Symposia on Molecular & Cellular Biology, 1993, Schlingensiepen et al. report of two homologues of the proto-oncogene c-jun which have been identified in mammals. In that abstract it is speculated that jun-B may play a role in cell-differentiation. In order to investigate functional questions of the jun-B gene antisense phosphorothioate oligodeoxynucleotides (S-ODN) have been used to specifically inhibit expression of c-jun and jun-B in neuronally differentiating PC-12 tumor cells in primary neuronal cell cultures from the rat hippocampus. Western blot analysis revealed specific reductions in the respective Jun protein levels by more than 90% after application of 2 μ M S-ODN. In neuronal cell cultures neurite outgrowth was strongly inhibited after inhibition of jun-B expression but was enhanced after application of anti c-jun-S-ODN. Even more drastic changes were observed in neuronally differentiating PC-12 tumor cells. The results suggest that jun-B plays a crucial role in cell differentiation while c-jun appears to

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inhibit differentiation. A therapeutic concept is also not available from that disclosure.

From Biomedicine & Pharmacotherapy, Abstract 38, from the 5. International Congress on Differentiation Therapy, Schlingensiepen et al. report also about the results published in Journal of Cellular Biochemistry.

In Developmental Genetics 14: 305 - 312 (1993) Schlingensiepen et al. report about the induction of the jun-B and/or c-jun transcription factors. The induction is part of the immediate early response to diverse stimuli that induce alterations in cellular programs. In order to determine functional significance of the jun-B and/or c-jun transcription antisense phosphorothioate oligodeoxynucleotides were used to inhibit the expression of the genes in proliferating and neuronally differentiating cells. In cell culture studies it was found that inhibition of jun-B expression markedly reduced morphological differentiation. Conversely, inhibition of c-jun proteins synthesis enhanced morphological differentiation of both primary neurons and PC-12 tumor cells.

EP-A-0 305 929 deals with membranes with bound oligonucleotides and peptides directly bound onto the membrane. The method for synthesizing oligonucleotides directly bound onto a membrane provides a means for generating membrane affinity supports. A modified membrane for the method of direct synthesis is also provided.

WO 92/15680 deals with a method and compositions for the selective inhibition of gene expression. Disclosed are methods and compositions for the selective inhibition gene expression through the application of antisense RNA technology. Antisense RNA constructs employ the use of antisense intron DNA corresponding to distinct intron regions of the gene whose expression is targeted for down-regulation. In

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an exemplary embodiment a human lung cancer cell line (NCI-H460a) with a homozygous spontaneous K-ras mutation was transfected with a recombinant plasmid that synthesizes a genomic segment of K-ras in antisense orientation. Translation of the mutated K-ras mRNA was specifically inhibited, whereas expression of H-ras and N-ras was unchanged. A three-fold growth inhibition occurred in H460a cells when expression of the mutated ras p21 protein was down-regulated by antisense RNA and cells remained viable. The growth of H460a tumors in nu/nu mice was substantially reduced by expressed K-ras antisense RNA.

Dan Mercola in Prospects for Antisense Nucleic Acid Therapy of Cancer and AIDS, pp. 83 - 114, 1991 deals with the use of antisense fos RNA and, to a lesser extent, antisense jun RNA. Such antisense RNA has contributed to understanding of the roles of gene products in cell cycle regulation, differentiation and so on. Progress in the application of antisense RNA and oligonucleotides to these topics and implications for diagnostic and therapeutic approaches are considered.

S. van den Berg in Prospects for Antisense Nucleic Acid Therapy and Cancer and AIDS, pp. 63 - 70, 1991 deals with antisense fos oligodeoxyribonucleotides suppressing the generation of chromosomal aberrations. The fast induction of the expression product FOS nuclear onco-protein by serum treatment of starved cells was used to test the functional stability of antisense oligodeoxyribonucleotides. Unmodified oligodeoxyribonucleotides lost their blocking effect with a half-life of about 2 hours, modification of the backbone by thioesters extended the half-life to about 4 hours. The modified oligodeoxyribonucleotides were used to unravel a decisive role of FOS in a complex physiologic event: The induction of chromosomal aberrations upon overexpression of oncogenes like ras and mos and upon irradiation of fibroblasts with UV-light.

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Induction of the c-Fos, Jun-B and/or c-Jun transcription factors is part of the immediate early response to diverse stimuli that induce alterations in cellular programs. C-jun and c-fos are proto-oncogenes whose expression is required for induction of cell proliferation while the function of the Jun-B transcription factor has remained unclear.

Neuronal cell injury and cell death due e. g. to hypoxia or hypoglycemia may occur in cause of responses of the cell to diverse stimuli inducing alterations in cellular programs.

It is an object of the present invention to provide a pharmaceutical composition for the prevention and/or treatment of neuronal injury and/or cell death. Surprisingly, the expression of the c-fos and c-jun gene plays a causal role in neuronal cell injury and cell death due e. g. to hypoxia or hypoglycemia.

Furthermore, surprisingly, expression of the Jun-B protein is required for the differentiation of normal and neoplastic cells and inhibition of c-Jun protein expression enhances the differentiation of such cells. Based on that result the present invention provides a pharmaceutical composition for the treatment of neoplasms by enhancing jun-B expression and/or inhibiting c-jun expression.

A pharmaceutical composition comprising antisense nucleic acids or effective derivatives thereof which hybridize with an area of the mRNAs or DNA comprising the genes for c-jun, c-fos or jun-B are able to solve the problems addressed above. The antisense nucleic acid is able to hybridize with regions of the c-jun, jun-B or c-fos mRNAs. It is understood by the skilled person that fragments of the antisense nucleic acids and antisense nucleic acids containing these sequences work according to the invention so long as production of the c-Jun and/or c-Fos and/or Jun-B proteins is reduced or inhibited.

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According to the invention the antisense-oligonucleotides are obtainable by solid phase synthesis using phosphite triester chemistry by growing the nucleotide chain in 3'-5' direction in that the respective nucleotide is coupled to the first nucleotide which is covalently attached to the solid phase comprising the steps of

- cleaving 5' DMT protecting group of the previous nucleotide,
- adding the respective nucleotide for chain propagation,
- modifying the phosphite group subsequently cap unreacted 5'-hydroxyl groups and
- cleaving the oligonucleotide from the solid support,
- followed by working up the synthesis product.

The chemical structures of oligodeoxy-ribonucleotides are given in figure 1 as well as the respective structures of antisense oligo-ribonucleotides are given in figure 2. The oligonucleotide chain is to be understood as a detail out of a longer nucleotide chain.

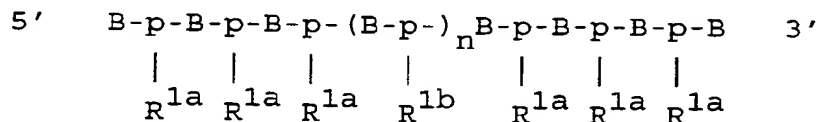
In figure 1 lit. B means an organic base such as adenine (A), guanine (G), cytosine (C) and thymine (T) which are coupled via N9(A,G) or N1(D,T) to the desoxyribose. The sequence of the bases is the reverse complement of the genetic target sequence (mRNA-sequence). The modifications used are

1. Oligodeoxy-ribonucleotides where all R^1 are substituted by

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- 1.1 $R^1 = O$
 1.2 $R^1 = S$
 1.3 $R^1 = F$
 1.4 $R^1 = CH_3$
 1.5 $R^1 = OEt$

2. Oligodeoxy-ribonucleotides where R^1 is varied at the internucleotide phosphates within one oligonucleotide



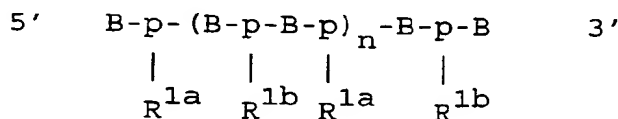
where B = deoxy-ribonucleotide dA, dC, dG or dT depending on gene sequence

p = internucleotide phosphate

n = an oligodeoxy-ribonucleotide stretch of length 6 - 20 bases

- 2.1 $R^{1a} = S$; $R^{1b} = O$
 2.2 $R^{1a} = CH_3$; $R^{1b} = O$
 2.3 $R^{1a} = S$; $R^{1b} = CH_3$
 2.4 $R^{1a} = CH_3$; $R^{1b} = S$

3. Oligodeoxy-ribonucleotides where R^1 is alternated at the internucleotide phosphates within one oligonucleotide



where B = deoxy-ribonucleotide dA, dC, dG or dT depending on gene sequence

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p = internucleotide phosphate

n = an oligodeoxy-ribodinucleotide stretch of
length 4 - 12 dinucleotides

3.2	$R^{1a} = S;$	$R^{1b} = O$
3.2	$R^{1a} = CH_3;$	$R^{1b} = O$
3.3	$R^{1a} = S;$	$R^{1b} = CH_3$

4. Any of the compounds 1.1 - 1.5; 2.1 - 2.4; 3.1 - 3.3 coupled at R^2 with the following compounds which are covalently coupled to increase cellular uptake

- 4.1 cholesterol
- 4.2 poly(L)lysine
- 4.3 transferrin
- 4.4 folic acid

5. Any of the compounds 1.1 - 1.5; 2.1 - 2.4; 3.1 - 3.3 coupled at R^3 with the following compounds which are covalently coupled to increase cellular uptake

- 5.1 cholesterol
- 5.2 poly(L)lysine
- 5.3 transferrin
- 5.4 folic acid

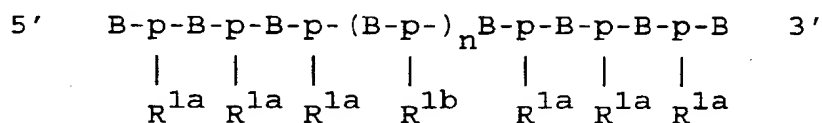
In the case of the RNA-oligonucleotides (figure 2) are the basis (adenine (A), guanine (G), cytosine (C), uracil (U)) coupled via N9 (A,G) or N1 (C,U) to the ribose. The sequence of the basis is the reverse complement of the genetic target sequence (mRNA-sequence). The modifications in the oligonucleotide sequence used are as follows

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6. Oligo-ribonucleotides where all R^1 are substituted by

- 6.1 $R^1 = O$
- 6.2 $R^1 = S$
- 6.3 $R^1 = F$
- 6.4 $R^1 = CH_3$
- 6.5 $R^1 = OEt$

7. Oligo-ribonucleotides where R^1 is varied at the internucleotide phosphates within one oligonucleotide



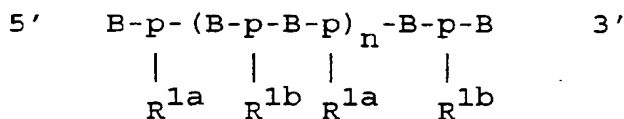
where B = ribonucleotide A, C, G or T depending
on gene sequence

p = internucleotide phosphate

n = an oligo-ribonucleotide stretch of length 4 -
20 bases

- 7.1 $R^{1a} = S$; $R^{1b} = O$
- 7.2 $R^{1a} = CH_3$; $R^{1b} = O$
- 7.3 $R^{1a} = S$; $R^{1b} = CH_3$
- 7.4 $R^{1a} = CH_3$; $R^{1b} = S$

8. Oligo-ribonucleotides where R^1 is alternated at the internucleotide phosphates within one oligonucleotide



where B = ribonucleotide A, C, G or T depending
on gene sequence

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p = internucleotide phosphate

n = an oligo-ribodinucleotide stretch of length
4 - 12 dinucleotides

8.2	$R^{1a} = S;$	$R^{1b} = O$
8.2	$R^{1a} = CH_3;$	$R^{1b} = O$
8.3	$R^{1a} = S;$	$R^{1b} = CH_3$

9. Any of the compounds 6.1 - 6.5; 7.1 - 7.4; 8.1 - 8.3 coupled at R^2 with the following compounds which are covalently coupled to increase cellular uptake

- 9.1 cholesterol
- 9.2 poly(L)lysine
- 9.3 transferrin

10. Any of the compounds 6.1 - 6.5; 7.1 - 7.4; 8.1 - 8.3 coupled at R^3 the following compounds are covalently coupled to increased cellular uptake

- 10.1 cholesterol
- 10.2 poly(L)lysine
- 10.3 transferrin

11. Any of the compounds 6.1 - 6.5; 7.1 - 7.4; 8.1 - 8.3; 9.1 - 9.3; 10.1 - 10.3 where all R^4 are substituted by

- 11.1 $R^4 = O$
- 11.2 $R^4 = F$
- 11.3 $R^4 = CH_3$

In a preferred embodiment the c-jun antisense nucleic acid comprising the sequences as identified in the sequence listing, Seq. ID. No. 1 - 55 and 174 - 177.

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In a preferred embodiment the jun-B antisense nucleic acids is comprising the sequences as identified in the sequence listing Seq. ID No. 56 - 97 and 178, 179.

In another preferred embodiment the c-fos antisense nucleic acid is comprising the sequences as identified in the sequence listing under Seq. ID No. 98 - 173 and 180 - 185.

It is possible that one single individual sequence as mentioned above works as an antisense nucleic acid or oligonucleotide structure according to the invention. However, it is also possible that one strand of nucleotides comprises more than one of the sequences as mentioned above directly covalently linked or with other nucleotides covalently linked inbetween. Preferably, individual oligonucleotides of the sequences as outlined in the sequence listing are addressed.

The sequence

5' GTCCCTATAC GAAC 3'

served as randomized control sequence.

In a preferred embodiment of these oligo-nucleotides they are phosphorotioate derivatives.

Modifications of the antisense-oligonucleotides are advantageous since they are not as fast destroyed by endogenous factors when applied as this is valid for naturally occurring nucleotide sequences. However, it is understood by the skilled person that also naturally occurring nucleotides having the disclosed sequence can be used according to the invention. In a very preferred embodiment the modification is a phosphorothioate modification.

The synthesis of the oligodeoxy-nucleotide of the invention is described as an example in a greater detail as follows.

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Oligodeoxy-nucleotides were synthesized by stepwise 5'-addition of protected nucleosides using phosphite triester chemistry. The nucleotide A was introduced as 5'-dimethoxytrityl-deoxyadenosine (N-benzoyl)-N,N'-diisopropyl-2-cyanoethyl phosphoramidite (0.1 M); C was introduced by a 5'-dimethoxytrityl-deoxycytidine (N⁴-benzoyl)-N,N'-diisopropyl-2-cyanoethyl phosphoramidite; G was introduced as 5'-dimethoxytrityl-deoxyguanosine (N⁸-isobutyryl)-N,N'-diisopropyl-2-cyanoethyl phosphoramidite and the T was introduced as 5'-dimethoxytrityl-deoxythymidine-N,N'-diisopropyl-2-cyanoethyl phosphoramidite. The nucleosides were preferably applied in 0.1 M concentration dissolved in acetonitrile.

Synthesis was performed on controlled pore glass particles of approximately 150 μm diameter (pore diameter 500 Å) to which the most 3' nucleoside is covalently attached via a long-chain alkylamin linker (average loading 30 $\mu\text{mol/g}$ solid support).

The solid support was loaded into a cylindrical synthesis column, capped on both ends with filters which permit adequate flow of reagents but hold back the solid synthesis support. Reagents were delivered and withdrawn from the synthesis column using positive pressure of inert gas. The nucleotides were added to the growing oligonucleotide chain in 3' \rightarrow 5' direction. Each nucleotide was coupled using one round of the following synthesis cycle:

Cleave 5'DMT (dimethoxytrityl) protecting group of the previous nucleotide with 3-chloroacetic acid in dichloromethane followed by washing the column with anhydrous acetonitrile. Then simultaneously one of the bases in form of their protected derivative depending on the sequence was added plus tetrazole in acetonitrile. After reaction the reaction mixture has been withdrawn and the phosphite was oxidized with a mixture of sulfur (S₈) in carbon disulfide/pyridine/-triethylamine. After the oxidation reaction the mixture was

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withdrawn and the column was washed with acetonitrile. The unreacted 5'-hydroxyl groups were capped with simultaneous addition of 1-methylimidazole and acetic anhydride/lutidine-/tetrahydrofuran. Thereafter, the synthesis column was washed with acetonitrile and the next cycle was started.

The work up procedure and purification of the synthesis products occurred as follows.

After the addition of the last nucleotide the deoxynucleotides were cleaved from the solid support by incubation in ammonia solution. Exocyclic base protecting groups were removed by further incubation in ammonia. Then the ammonia was evaporated under vacuum. Full-length synthesis products still bearing the 5'DMT protecting group were separated from shorter failure contaminants using reverse phase high performance liquid chromatography on silica C₁₈ stationary phase. Eluents from the product peak were collected, dried under vacuum and the 5'-DMT protecting group cleaved by incubation in acetic acid which was evaporated thereafter under vacuum. The synthesis products were solubilized in the deionized water and extracted three times with diethylether. Then the products were dried in vacuo. Another HPLC-AX chromatography was performed and the eluents from the product peak were dialysed against excess of Trisbuffer as well as a second dialysis against deionized water. The final products were lyophilized and stored dry.

The antisense nucleic acids of the invention are intermediate products of the pharmaceutical composition or medicament of the invention. This medicament can be used for treating and/or preventing neuronal cell death, for treating neoplasms in which the expression of c-jun and/or jun-B or c-fos is of relevance for the pathogenicity. The pharmaceutical composition may comprise besides the effective compound(s) suitable carrier agents, solvents and other ingredients known in the art for producing medicaments. Preferably, these

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agents facilitate the administration of the pharmaceutical composition of the invention. Typically, the pharmaceutical composition is administered as i.v. infusion or i.v. bolus injection. The amount of the active ingredient to be administered is typically in the range of 0.2 - 50 mg of the oligonucleotide per kg body weight per day, in particular 1 - 12 mg/kg body weight per day.

The effect of antisense oligo-nucleotides specific for c-jun, jun-B and c-fos on protection against neuronal cell death was investigated. It was demonstrated that that c-fos as well as c-jun play a causal role in neuronal cell death. Also the role of these genes in the differentiation and proliferation of neoplastic cells was investigated. It was demonstrated that inhibition of c-Jun protein synthesis could enhance differentiation of neoplastic cells. It was demonstrated that antisense oligodeoxynucleotides as well as phosphorothioate modified nucleic acids, complementary to the mRNAs of c-jun, jun-B and c-fos specifically inhibit expression of the respective proteins.

In principal the compound which can be used as an active compound in the pharmaceutical composition can be used as a diagnostic tool for evaluating whether the respective genes are expressed. Typically, a radio active label nucleotides are hybridized by the method of northern blotting with is well-known in the art or in situ with a sample to be examined. The degree of hybridization is a measure for the degree of expression of the respective genes.

Figure 3

Western blot analysis of rat PC-12 cell lysates. Effects of different phosphorothioate oligodeoxynucleotides on c-Fos protein expression. Incubation time with oligodeoxynucleotide were 6 h. Lane 1: randomized control S-ODN; Lane 2: anti-c-

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fos S-ODN-180; Lane 3: anti-c-fos S-ODN-182. 10 μ g of total protein were used per lane.

Figure 4

Effects of different phosphorothioate oligodeoxynucleotides on c-Jun and Jun-B protein expression. A: Western blots of NIH 3T3 cell lysate probed with an anti-c-jun antibody. B: SK-BR3 cell lysates, probed with an anti-jun-B antibody.

Incubation times with oligodeoxynucleotide were: Lanes 1 - 3: 6 h; Lanes 4 - 6: 24 h. Lanes 1 and 4: randomized control S-ODN; Lanes 2 and 5: anti-jun-B S-ODN-62; Lane 3 and 6: anti-c-jun S-ODN-13. 10 μ g of total protein were used per lane.

Figure 5

Effects of different phosphorothioate oligodeoxynucleotides on c-Jun, Jun-B and c-Fos protein expression.

A: Enzyme-linked immunosorbent assay of rat PC-12 cell lysates incubated with c-jun (rat specific) antisense oligodeoxynucleotides 174, 175, 176, 177.

B: Enzyme-linked immunosorbent assay of human SK-Br-3 cell lysates incubated with c-jun (human-specific) antisense oligodeoxynucleotides 1, 7, 13, 17, 20, 23, 26, 31, 31, 39, 45, 51 or 54.

C: Enzyme-linked immunosorbent assay of rat PC-12 cell lysates incubated with jun-B (rat-specific) antisense oligodeoxynucleotides 178 or 179.

D: Enzyme-linked immunosorbent assay of human SK-Br-3 cell lysates incubated with jun-B (human-specific) antisense oligodeoxynucleotides 57, 62, 64, 69, 80 85, 89, 92, 95 or 97.

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E: Enzyme-linked immunosorbent assay of rat PC-12 cell lysates incubated with c-fos (rat-specific) antisense oligodeoxynucleotides 180, 181, 182, 183, 184 or 185.

F: Enzyme-linked immunosorbent assay of human SK-Br-3 cell lysates incubated with c-fos (human-specific) antisense oligonucleotides 98, 99, 102, 103, 108, 116, 121, 130, 139, 144, 152, 158, 165, 170 or 173.

Phosphorothioate-oligodeoxynucleotides were used at 2 μ M concentration. Control cells were left untreated (white bars) or treated with 2 μ M of randomized control phosphorothioate oligonucleotides (grey bars).

Figure 6

Survival of rat cerebellar neurons following hypoxia. Phosphorothioate oligonucleotides were used at 1 μ M concentration. Control cells were not subjected to hypoxia (white bar). Hypoxia control cells were either not treated with oligonucleotide (black bar, C) or treated with the same concentration of randomized control phosphorothioate oligodeoxynucleotide (grey bar). Error bars correspond to 1 SD.

Figure 7

Enhanced proliferation arrest after suppression of c-Jun protein synthesis and lack of proliferation arrest in NGF treated PC-12 cells after suppression of Jun-B protein synthesis. PC-12 cell number after 8 days of NGF treatment. Bars represent the mean of 4 values. Grey bars: 2 μ M randomized control S-ODN; White bars: 2 μ M anti-c-jun S-ODN-174; Black bars: 2 μ M anti-jun-B S-ODN-179. Error bars correspond to 1 SD.

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Figure 8

Morphological differentiation of NGF treated PC-12 cells after inhibition of c-jun or jun-B protein synthesis.

A: Control cells not treated with phosphorothioate oligodeoxynucleotides.

B: Cells incubated with 2 μ M anti-jun-B S-ODN-179.

C: Cells incubated with 2 μ M anti-c-jun S-ODN-174.

The invention is further explained by the following non-limiting examples.

Example 1

Cell Lines and Proliferation Assays

NIH 3T3 mouse fibroblasts and SK-Br-3 human mammary carcinoma cells were grown in RPMI medium (Gibco) supplemented with 100 U/ml penicillin, 100 μ g/ml streptomycin, 5% FCS. PC-12 rat pheochromocytoma cells were grown in Dulbecco's modified Eagle's medium (DMEM medium Seromed), supplemented with 100 U/ml penicillin, 100 μ g/ml streptomycin, 5% FCS.

Example 2

Western Blot

Cells were kept under low serum conditions in RPMI / 2% FCS for 3 days, trypsinized and preincubated in RPMI/5% FCS/2 μ M S-ODN for 5 min. 3×10^6 cells were plated into 260 ml culture flasks and grown for the times indicated in RPMI/5% FCS/2 μ M S-ODN, trypsinized, spun down and lysed by freezing. SDS-polyacrylamide gel electrophoresis, blotting and chemiluminescence detection were performed according to standard techniques. Blots were probed with a rabbit anti mouse-c-jun antibody (Oncogene Science) or with a rabbit anti human-jun-B antibody (Oncogene Science) or with a rabbit anti-c-fos

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antibody (Oncogene Science), using goat anti-rabbit IgG-alkaline-phosphatase conjugate (Boehringer Mannheim) as second antibody and CSPD (Tropix) for chemiluminescent detection.

Example 3

Enzyme-linked immunosorbent assay (ELISA)

Cell lysates were diluted in 50 mM carbonate buffer at pH 9.0 and immobilized on immunon II plates (Dynatech Laboratories, Inc.) overnight. Antigen solution was removed and 200 μ l/well phosphate buffered saline (PBS)/1%BSA/0.02% azide were added to block non-specific protein binding. Following incubation at room temperature for 2 h solution was removed. After washing with PBS plates were air dried for 3 h. Specific antibodies for c-jun, jun-B or c-fos (Oncogene, Santa Cruz, Biotechnology Inc.) were added at 50 μ l/well, diluted in blocking buffer. Following 1 h incubation at room temperature samples were removed and subsequently wells were washed four times with PBS/0.05% Tween 20. Then 50 μ l of secondary antibody-phosphatase conjugate were added and removed after 1 h. Wells were washed with diethanolamine buffer (10 mM diethanolamine, 0.5 mM $MgCl_2$, pH 9.5). 1 tablet of Sigma 104 phosphatase substrate was dissolved in 5 ml diethanolamine buffer. 50 μ l of the substrate solution were added per well. The reaction was stopped with 50 μ l 0.1 M EDTA (pH 7.5) and plates were read on a microtitration plate reader.

Example 4

Neuronal Survival

Cerebella were removed from the brains of 8 day old rats under sterile conditions and were transferred into 0.1 % trypsin, 0.1% DNase in phosphate buffered saline/glucose solution for 15 min. at 20°C, followed by 1.5 % soybean

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trypsin inhibitor (Sigma) for 5 min. Cells were dissociated in a mixture of Dulbecco's modified Eagle's medium and Ham's F-12 medium (50%/50%, v/v; DMEM F-12, Gibco) supplemented with KCl 25 mM, penicillin (5 U/ml), gentamycin (5 μ g/ml) and 30 mM glucose. Cells were centrifuged at 300 x g for 3 min, and resuspended in the same medium, supplemented with 10% fetal calf serum (Gibco). Cells were plated in 3 cm dishes (0.5 ml per well) coated with poly-L-lysine (10 μ g/ml, Sigma) to a density of 1×10^5 cells/well and transferred to an incubator with humidified atmosphere with 95% O₂/5% CO₂. Cytosine arabinoside (40 μ M) was added after 24 h to inhibit glial cell proliferation. On day 16 after seeding, cells were exposed to anoxia for 16 h by placing them in a hermetic chamber containing a humidified atmosphere with 95% N₂/5% CO₂. The chamber was transferred into an incubator at 37°C. Phosphorothioate oligodeoxynucleotides were added at 1 μ M concentration 8 h before the onset of anoxia. Neuronal cell injury was determined 26 h later by staining with trypan blue dye exclusion (incubation with 0.4% trypan blue for 5 min).

Example 5

Proliferation of PC-12 cells after treatment with NGF and different phosphorothioate oligodeoxynucleotides.

PC-12 cells were plated at a density of 2,500 cells/well in DMEM (Seromed) supplemented with 100 U/ml penicillin, 100 μ g/ml streptomycin, 5% FCS/2 μ M S-ODN. 2 μ M S-ODNs were added 6 h after plating. 24 h after plating, cells were incubated with 10 ng/ml of the 2.5 S subfraction of nerve growth factor (NGF) (Boehringer Mannheim) for 8 days. Cell number was determined by using trypan blue dye exclusion (incubation with 0.4 % trypan blue for 5 min) and counting of cells in a Neubauer counting chamber.

Example 6

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PC-12 tumor cell differentiation

PC-12 cells were plated at a density of 2,500 cells/well (Seromed) into 96 well microtitration plates coated with poly-L-lysine (10 $\mu\text{g/ml}$, Sigma) in 100 μl of DMEM supplemented with 100 U/ml penicillin, 100 $\mu\text{g/ml}$ streptomycin, 5% FCS, S-ODNs were added at 2 μM concentration 2 h after plating. 6 h after plating, cells were incubated with 40 ng/ml of the 2.5 S subfraction of nerve growth factor (NGF) (Boehringer Mannheim) for 11 days.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

- (A) NAME: Biognostik Gesellschaft fuer
molekularbiologische Diagnostik mbH
- (B) STREET: Carl-Giesecke-Str. 3
- (C) CITY: Goettingen
- (E) COUNTRY: Germany
- (F) POSTAL CODE (ZIP): 37079

(ii) TITLE OF INVENTION: A pharmaceutical composition comprising antisense-nucleic acid for prevention and/or treatment of neuronal injury, degeneration and cell death and for the treatment of neoplasms

(iii) NUMBER OF SEQUENCES: 185

(iv) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Floppy disk
- (B) COMPUTER: IBM PC compatible
- (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(2) INFORMATION FOR SEQUENCE ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

TCGGACTATA CTGC

14

(2) INFORMATION FOR SEQUENCE ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

CAGTTCGGAC TATACT

16

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(2) INFORMATION FOR SEQUENCE ID NO: 3:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

AAGCCTAAGA CGCA

14

(2) INFORMATION FOR SEQUENCE ID NO: 4:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

GCCCAAGTTC AACA

14

(2) INFORMATION FOR SEQUENCE ID NO: 5:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

TGAAAAGTCG CGGT

14

(2) INFORMATION FOR SEQUENCE ID NO: 6:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:
GGTTAATTAA GATGCCTC 18
- (2) INFORMATION FOR SEQUENCE ID NO: 7:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: unknown
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:
TCTCTAAGAG CGCA 14
- (2) INFORMATION FOR SEQUENCE ID NO: 8:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: unknown
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:
ACGTGAGGTT AGTTTG 16
- (2) INFORMATION FOR SEQUENCE ID NO: 9:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: unknown
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:
CACGTGAGGT TAGT 14
- (2) INFORMATION FOR SEQUENCE ID NO: 10:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: unknown
 (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)

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(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

CATAGAACAG TCCG

14

(2) INFORMATION FOR SEQUENCE ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CAGTCATAGA ACAGTC

16

(2) INFORMATION FOR SEQUENCE ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

CTTTGCAGTC ATAGAACA

18

(2) INFORMATION FOR SEQUENCE ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

TGCAGTCATA GAAC

14

(2) INFORMATION FOR SEQUENCE ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GGTCGTTTCC ATCT

14

(2) INFORMATION FOR SEQUENCE ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

CATAGAAGGT CGTTTC

16

(2) INFORMATION FOR SEQUENCE ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

CGTCATAGAA GGTC

14

(2) INFORMATION FOR SEQUENCE ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

CATCGTCATA GAAGG

15

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(2) INFORMATION FOR SEQUENCE ID NO: 18:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 24 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

GGACGGGAGG AACGAGGCGT TGAG

24

(2) INFORMATION FOR SEQUENCE ID NO: 19:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

TAGCCATAAG GTCC

14

(2) INFORMATION FOR SEQUENCE ID NO: 20:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

GGTTACTGTA GCCA

14

(2) INFORMATION FOR SEQUENCE ID NO: 21:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:
GGTTACTGTA GCCA 14
- (2) INFORMATION FOR SEQUENCE ID NO: 22:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:
CAGGGTCATG CTCTGTTTCA GGATCTTGGG 30
- (2) INFORMATION FOR SEQUENCE ID NO: 23:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:
AGTTCTTGGC GCGGAGGT 18
- (2) INFORMATION FOR SEQUENCE ID NO: 24:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:
AGGTGAGGAG GTCCGAGT 18
- (2) INFORMATION FOR SEQUENCE ID NO: 25:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)

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(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

TGGACTGGAT TATCAG

16

(2) INFORMATION FOR SEQUENCE ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

GTGGTG GTGA TGTGCCCG

18

(2) INFORMATION FOR SEQUENCE ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

TGTCACG TTC TTGG

14

(2) INFORMATION FOR SEQUENCE ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

CTCATCTGTC ACGT

14

(2) INFORMATION FOR SEQUENCE ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

- 29 -

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

CGAAGCCCTC GCGAACC

18

(2) INFORMATION FOR SEQUENCE ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

GCGTGTTCTG GCTGTGCAGT TCGG

24

(2) INFORMATION FOR SEQUENCE ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

CTGCCCGTT GACC

14

(2) INFORMATION FOR SEQUENCE ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

AGGTTTGCGT AGAC

14

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(2) INFORMATION FOR SEQUENCE ID NO: 33:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

GGTTGAAGTT GCTG

14

(2) INFORMATION FOR SEQUENCE ID NO: 34:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

CTGGGTTGAA GTTG

14

(2) INFORMATION FOR SEQUENCE ID NO: 35:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 24 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

TGCTGGGGTT GCGCGGAAA GGCC

24

(2) INFORMATION FOR SEQUENCE ID NO: 36:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:
TGCTGCACGG GCATCTGCTG 20
- (2) INFORMATION FOR SEQUENCE ID NO: 37:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:
GGCACTGTCT GAGGCTCCTC CTTCAGG 27
- (2) INFORMATION FOR SEQUENCE ID NO: 38:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:
ACTCCATGTC GATG 14
- (2) INFORMATION FOR SEQUENCE ID NO: 39:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:
CTCTCCGCCT TGATCC 16
- (2) INFORMATION FOR SEQUENCE ID NO: 40:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)

- 32 -

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

GTTCTCATG CGCTTC

16

(2) INFORMATION FOR SEQUENCE ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

CTGAGCTTTC AAGG

14

(2) INFORMATION FOR SEQUENCE ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

GCGATTCTCT CCAGCTTCCT TTTTCG

26

(2) INFORMATION FOR SEQUENCE ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

CTGAGCTTTC AAGGTTTTCA CTTTTTCCTC

30

(2) INFORMATION FOR SEQUENCE ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

TCCCTGAGCA TGTT

14

(2) INFORMATION FOR SEQUENCE ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

TCTGTTTAAG CTGTGC

16

(2) INFORMATION FOR SEQUENCE ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

CTTCTGTTT AAGCTGTG

18

(2) INFORMATION FOR SEQUENCE ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

GGTTCATGAC TTTCTG

16

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(2) INFORMATION FOR SEQUENCE ID NO: 48:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

CGTGGTTCAT GACT

14

(2) INFORMATION FOR SEQUENCE ID NO: 49:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

ACTGTTAACG TGGTTC

18

(2) INFORMATION FOR SEQUENCE ID NO: 50:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

CCTACTGTAA CGTG

14

(2) INFORMATION FOR SEQUENCE ID NO: 51:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

CCCCTGTGTTA ACGT

14

(2) INFORMATION FOR SEQUENCE ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

AGCATGAGTT GGCA

14

(2) INFORMATION FOR SEQUENCE ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

GCGTTAGCAT GAGT

14

(2) INFORMATION FOR SEQUENCE ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

GTTTGCAACT GCTG

14

(2) INFORMATION FOR SEQUENCE ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

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(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

CAAAATGTTT GCAACTGC

18

(2) INFORMATION FOR SEQUENCE ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

TCCATTTTAG TGCACATC

18

(2) INFORMATION FOR SEQUENCE ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

CTGTTCCATT TTAGTGCA

18

(2) INFORMATION FOR SEQUENCE ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

GTGTATGAGT CGTC

14

(2) INFORMATION FOR SEQUENCE ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

CTGTGTATGA GTCG

14

(2) INFORMATION FOR SEQUENCE ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

CGTAGCTGTG TATG

14

(2) INFORMATION FOR SEQUENCE ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

TCGTGTAGAG AGAG

14

(2) INFORMATION FOR SEQUENCE ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

AGTTTGTAGT CGTGTAGA

18

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(2) INFORMATION FOR SEQUENCE ID NO: 63:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

GTTTGTAGTC GTGTAG

16

(2) INFORMATION FOR SEQUENCE ID NO: 64:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

AGTTTGTAGT CGTG

14

(2) INFORMATION FOR SEQUENCE ID NO: 65:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

GGAGTTTGTGTA GTCG

14

(2) INFORMATION FOR SEQUENCE ID NO: 66:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

TCAGGAGTTT GTAGTC

16

(2) INFORMATION FOR SEQUENCE ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

GTTTCAGGAG TTTGTAGT

18

(2) INFORMATION FOR SEQUENCE ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

TCGGTTTCAG GAGT

14

(2) INFORMATION FOR SEQUENCE ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

TTGAGACTCC GGTA

14

(2) INFORMATION FOR SEQUENCE ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

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(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

ACCAGAAAAG TAGCTG

16

(2) INFORMATION FOR SEQUENCE ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

CCTGACCAGA AAAG

14

(2) INFORMATION FOR SEQUENCE ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

ATTCAGGCGT TCCA

14

(2) INFORMATION FOR SEQUENCE ID NO: 73:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

CTGTTGGGGA CAAT

14

(2) INFORMATION FOR SEQUENCE ID NO: 74:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

GGTAAAAGTA CTGTCC

16

(2) INFORMATION FOR SEQUENCE ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

GGGTAAAAGT ACTGTC

16

(2) INFORMATION FOR SEQUENCE ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

GCACCTCCAC CGCTGCCA

18

(2) INFORMATION FOR SEQUENCE ID NO: 77:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

CTCCTGCTCC TCGGTGAC

18

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(2) INFORMATION FOR SEQUENCE ID NO: 78:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

GCTTTGACAA AGCC

14

(2) INFORMATION FOR SEQUENCE ID NO: 79:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

CTTGTGCAGA TCGT

14

(2) INFORMATION FOR SEQUENCE ID NO: 80:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

TCATCTTGTG CAGATC

16

(2) INFORMATION FOR SEQUENCE ID NO: 81:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:
GTTTCATCTTG TGCAGA 16
- (2) INFORMATION FOR SEQUENCE ID NO: 82:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:
CGTGGTTCAT CTTG 14
- (2) INFORMATION FOR SEQUENCE ID NO: 83:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:
TCACGTGGTT CATC 14
- (2) INFORMATION FOR SEQUENCE ID NO: 84:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:
GCCCAGGGAC ACGTTGGG 18
- (2) INFORMATION FOR SEQUENCE ID NO: 85:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)

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(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

GGTTGGTGTA AACG

14

(2) INFORMATION FOR SEQUENCE ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

TACGAGCTCC CGGTCCCGAC

20

(2) INFORMATION FOR SEQUENCE ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

TAGCTGATGG TGGT

14

(2) INFORMATION FOR SEQUENCE ID NO: 88:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

CAGCTGCGCC GGGTGGCCAC CGGCGAAGGG

30

(2) INFORMATION FOR SEQUENCE ID NO: 89:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

TCCTTGAAGG TGGA

14

(2) INFORMATION FOR SEQUENCE ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

TCTTCCATGT TGATGG

16

(2) INFORMATION FOR SEQUENCE ID NO: 91:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

CTTTGATGCG CTCT

14

(2) INFORMATION FOR SEQUENCE ID NO: 92:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

CTCCACTTTG ATGC

14

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(2) INFORMATION FOR SEQUENCE ID NO: 93:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

GCTCCAGCTT CCGCTTCCGG CACTTGGTGG

30

(2) INFORMATION FOR SEQUENCE ID NO: 94:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

GGCCTTGAGC GTCTTCACCT TGTCTCCAG

30

(2) INFORMATION FOR SEQUENCE ID NO: 95:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

TGACCTTCTG TTTGAG

16

(2) INFORMATION FOR SEQUENCE ID NO: 96:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:
CATGACCTTC TGTTTG 16
- (2) INFORMATION FOR SEQUENCE ID NO: 97:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:
GTCATGACCT TCTG 14
- (2) INFORMATION FOR SEQUENCE ID NO: 98:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:
CGAGAACATC ATCG 14
- (2) INFORMATION FOR SEQUENCE ID NO: 99:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:
GTAGTCTGCG TTGA 14
- (2) INFORMATION FOR SEQUENCE ID NO: 100:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)

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(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

GCTGCAGCGG GAGGATGACG

20

(2) INFORMATION FOR SEQUENCE ID NO: 101:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

AGTAAGAGAG GCTATC

16

(2) INFORMATION FOR SEQUENCE ID NO: 102:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

GTAAGTAAGAG AGGC

14

(2) INFORMATION FOR SEQUENCE ID NO: 103:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

GGTAGTAAGA GAGG

14

(2) INFORMATION FOR SEQUENCE ID NO: 104:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

GTGAGTGGTA GTAAGA

16

(2) INFORMATION FOR SEQUENCE ID NO: 105:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

GTCCGTGCAG AAGTCCTG

18

(2) INFORMATION FOR SEQUENCE ID NO: 106:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

GAATGAAGTT GGCAC

16

(2) INFORMATION FOR SEQUENCE ID NO: 107:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

GGAATGAAGT TGGC

14

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(2) INFORMATION FOR SEQUENCE ID NO: 108:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

GGGAATGAAG TTGG

14

(2) INFORMATION FOR SEQUENCE ID NO: 109:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:

GCTGCACCAG CCACTGCAGG TCCGGACTGG

30

(2) INFORMATION FOR SEQUENCE ID NO: 110:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:

CTGGTCTGCG ATGGGGCCAC AGAGGAGACG

30

(2) INFORMATION FOR SEQUENCE ID NO: 111:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:
TCATGGTCTT CACAAC 16
- (2) INFORMATION FOR SEQUENCE ID NO: 112:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:
CAATGCTCTG CGCTCGGCCT CCTGTCATGG 30
- (2) INFORMATION FOR SEQUENCE ID NO: 113:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:
CTAGAGTTCC TCAC 14
- (2) INFORMATION FOR SEQUENCE ID NO: 114:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:
GAGTACGCTA GAGT 14
- (2) INFORMATION FOR SEQUENCE ID NO: 115:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)

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(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

GAAGAGTACG CTAG

14

(2) INFORMATION FOR SEQUENCE ID NO: 116:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

CTGCTTCCCA CCCAGCCCC ACATTCCC

30

(2) INFORMATION FOR SEQUENCE ID NO: 117:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

TTCATCCTCT GTACTGGGCT

20

(2) INFORMATION FOR SEQUENCE ID NO: 118:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:

GTTACGGATG TGCA

14

(2) INFORMATION FOR SEQUENCE ID NO: 119:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

CAGTTACGGA TGTG

14

(2) INFORMATION FOR SEQUENCE ID NO: 120:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

CCAGTTACGG ATGT

14

(2) INFORMATION FOR SEQUENCE ID NO: 121:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

AGAGTCTGAG TTGG

14

(2) INFORMATION FOR SEQUENCE ID NO: 122:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

GTGAGACTCA GAGT

14

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(2) INFORMATION FOR SEQUENCE ID NO: 123:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:

TCTTAGGGTG AGAC

14

(2) INFORMATION FOR SEQUENCE ID NO: 124:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

GAGAGTACTT CTTAGG

16

(2) INFORMATION FOR SEQUENCE ID NO: 125:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125:

GGAAGAACT ATGAGAGT

18

(2) INFORMATION FOR SEQUENCE ID NO: 126:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:
CTTAGGGAAG AAACATATG 18
- (2) INFORMATION FOR SEQUENCE ID NO: 127:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:
CGGTAAGAAA CTTAGG 16
- (2) INFORMATION FOR SEQUENCE ID NO: 128:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:
AGCATGCGGT AAGA 14
- (2) INFORMATION FOR SEQUENCE ID NO: 129:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:
GTCTGAAAGC ATGC 14
- (2) INFORMATION FOR SEQUENCE ID NO: 130:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)

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(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:

AGAACAAAGA AGAGCC

16

(2) INFORMATION FOR SEQUENCE ID NO: 131:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:

CAAGAGAACA AAGAAGAG

18

(2) INFORMATION FOR SEQUENCE ID NO: 132:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132:

CAGCAAGAGA ACAAAG

16

(2) INFORMATION FOR SEQUENCE ID NO: 133:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133:

TCCTCAGCAA GAGA

14

(2) INFORMATION FOR SEQUENCE ID NO: 134:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134:

AGGTGTGACT TGCA

14

(2) INFORMATION FOR SEQUENCE ID NO: 135:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:

GAATAGGTGT GACTTG

16

(2) INFORMATION FOR SEQUENCE ID NO: 136:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136:

CAGAATAGGT GTGACT

16

(2) INFORMATION FOR SEQUENCE ID NO: 137:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:

GCAGAATAGG TGTG

14

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(2) INFORMATION FOR SEQUENCE ID NO: 138:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:

CAGTTGCAGA ATAGGT

16

(2) INFORMATION FOR SEQUENCE ID NO: 139:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:

GAAACCATT CTGACC

16

(2) INFORMATION FOR SEQUENCE ID NO: 140:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:

TGTGAAACCA TTTCTGAC

18

(2) INFORMATION FOR SEQUENCE ID NO: 141:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:
CACTGTGAAA CCATTCT 18
- (2) INFORMATION FOR SEQUENCE ID NO: 142:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:
CCACTGTGAA ACCA 14
- (2) INFORMATION FOR SEQUENCE ID NO: 143:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 143:
AGAACTGGCT CCTGCAGCTT CCCTGCTTCC 30
- (2) INFORMATION FOR SEQUENCE ID NO: 144:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown
 - (ii) MOLECULE TYPE: DNA (genomic)
 - (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144:
CACCTCCATT CACCC 15
- (2) INFORMATION FOR SEQUENCE ID NO: 145:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown
 - (ii) MOLECULE TYPE: DNA (genomic)

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- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145:
CAGTAAAAGT GTCTGC 16
- (2) INFORMATION FOR SEQUENCE ID NO: 146:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146:
CGACATTCAG TAAAAGTG 18
- (2) INFORMATION FOR SEQUENCE ID NO: 147:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 147:
GACCGACATT CAGT 14
- (2) INFORMATION FOR SEQUENCE ID NO: 148:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 148:
CTTCTGGAGA TAACTAGA 18
- (2) INFORMATION FOR SEQUENCE ID NO: 149:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:

CATCTTATTC CTTTCCCT

18

(2) INFORMATION FOR SEQUENCE ID NO: 150:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 150:

CAGCCATCTT ATTCCT

16

(2) INFORMATION FOR SEQUENCE ID NO: 151:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 151:

TGCAGCCATC TTATTC

16

(2) INFORMATION FOR SEQUENCE ID NO: 152:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 152:

GAGTGTATCA GTCAG

15

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(2) INFORMATION FOR SEQUENCE ID NO: 153:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 153:

GGAGTGTATC AGTC

14

(2) INFORMATION FOR SEQUENCE ID NO: 154:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 154:

CTTGGAGTGT ATCAGT

16

(2) INFORMATION FOR SEQUENCE ID NO: 155:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 155:

ACAGAGTACC TACC

14

(2) INFORMATION FOR SEQUENCE ID NO: 156:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 156:
CCAACCTTCC CTTAAG 16
- (2) INFORMATION FOR SEQUENCE ID NO: 157:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 157:
CCTTATGCTC AATCTC 16
- (2) INFORMATION FOR SEQUENCE ID NO: 158:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 158:
GTCTTACTCA AGGG 14
- (2) INFORMATION FOR SEQUENCE ID NO: 159:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 159:
ACAGTCTTAC TCAAGG 16
- (2) INFORMATION FOR SEQUENCE ID NO: 160:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)

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- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 160:
CATAAGACAC AGTCTTAC 18
- (2) INFORMATION FOR SEQUENCE ID NO: 161:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 161:
GAAAGCATAA GACACAGT 18
- (2) INFORMATION FOR SEQUENCE ID NO: 162:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 162:
GGAAAGCATA AGACAC 16
- (2) INFORMATION FOR SEQUENCE ID NO: 163:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 163:
AGGGATAAAG GAAAGC 16
- (2) INFORMATION FOR SEQUENCE ID NO: 164:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 164:

CCTGTATACA GAGG

14

(2) INFORMATION FOR SEQUENCE ID NO: 165:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 165:

TGTCTCCTGT ATACAG

16

(2) INFORMATION FOR SEQUENCE ID NO: 166:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 166:

CATCTTCTAG TTGGTC

16

(2) INFORMATION FOR SEQUENCE ID NO: 167:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 167:

CTCATCTTCT AGTTGG

16

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(2) INFORMATION FOR SEQUENCE ID NO: 168:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 168:

CTTCTCATCT TCTAGTTG

18

(2) INFORMATION FOR SEQUENCE ID NO: 169:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 169:

CAAAGCAGAC TTCTCA

16

(2) INFORMATION FOR SEQUENCE ID NO: 170:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 170:

CTGCAAAGCA GACT

14

(2) INFORMATION FOR SEQUENCE ID NO: 171:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 171:
CTAGTTTTTC CTTCTCCT 18
- (2) INFORMATION FOR SEQUENCE ID NO: 172:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 172:
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- (2) INFORMATION FOR SEQUENCE ID NO: 173:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 173:
CAGGATGAAC TCTAGT 16
- (2) INFORMATION FOR SEQUENCE ID NO: 174:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)
- (iii) ANTI-SENSE: YES
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(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown
- (ii) MOLECULE TYPE: DNA (genomic)

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(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 175:

AGGGTTACTG TAGC

14

(2) INFORMATION FOR SEQUENCE ID NO: 176:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 176:

GTAGTGGTGA TGTG

14

(2) INFORMATION FOR SEQUENCE ID NO: 177:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 177:

CGTCGTAGAA GGTC

14

(2) INFORMATION FOR SEQUENCE ID NO: 178:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 178:

TTTCGTGCAC ATCC

14

(2) INFORMATION FOR SEQUENCE ID NO: 179:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: unknown
- (D) TOPOLOGY: unknown

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(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 179:

AGTTTGTAGT CGTGAAGA

18

(2) INFORMATION FOR SEQUENCE ID NO: 180:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 180:

CGAGAACATC ATGG

14

(2) INFORMATION FOR SEQUENCE ID NO: 181:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 181:

GTAGTAGGAA AGGC

14

(2) INFORMATION FOR SEQUENCE ID NO: 182:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: unknown

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 182:

GGTAGTAGGA AAGG

14

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(2) INFORMATION FOR SEQUENCE ID NO: 183:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 14 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 183:

GGAATGGTAG TAGG

14

(2) INFORMATION FOR SEQUENCE ID NO: 184:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 184:

GGTCATTGAG AAGAG

15

(2) INFORMATION FOR SEQUENCE ID NO: 185:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: unknown
 - (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 185:

GCTAATGTTC TTGACC

16

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C l a i m s

1. A pharmaceutical composition comprising an effective amount of a compound which is capable from preventing and treating neuronal injury, degeneration, cell death and/or neoplasms in which expression of c-jun, c-fos or jun-B plays a causal role which compound being an antisense nucleic acid or effective derivative thereof, said antisense nucleic acid hybridizing with an area of the messenger RNA (mRNA) and/or DNA comprising the genes c-jun, c-fos or jun-B.
2. The pharmaceutical composition of claim 1 wherein the c-jun antisense nucleic acid or nucleotide is comprising the sequences as identified in the sequence listing under Seq. ID No. 1 - 55 and 174 - 177

the jun-B antisense nucleic acid comprising the sequence as identified in sequence listing under Seq. ID No. 56 - 97 and 178 - 179,

and the c-fos antisense nucleic acid comprising the sequence as identified in the sequence listing under Seq. ID No. 98 - 173 and 180 - 185,

wherein any sequence listed above represents a single oligonucleotide or represents a section of linked nucleotides in an nucleic acid and/or a nucleic acid comprising at least one of the above listed nucleotide sequences directly covalently linked or with other nucleotides separating the nucleotide sequences listed above.

3. The pharmaceutical composition of claims 1 and/or 2, wherein the oligonucleotides are modified oligonucleotides such as phosphorothioate derivatives.

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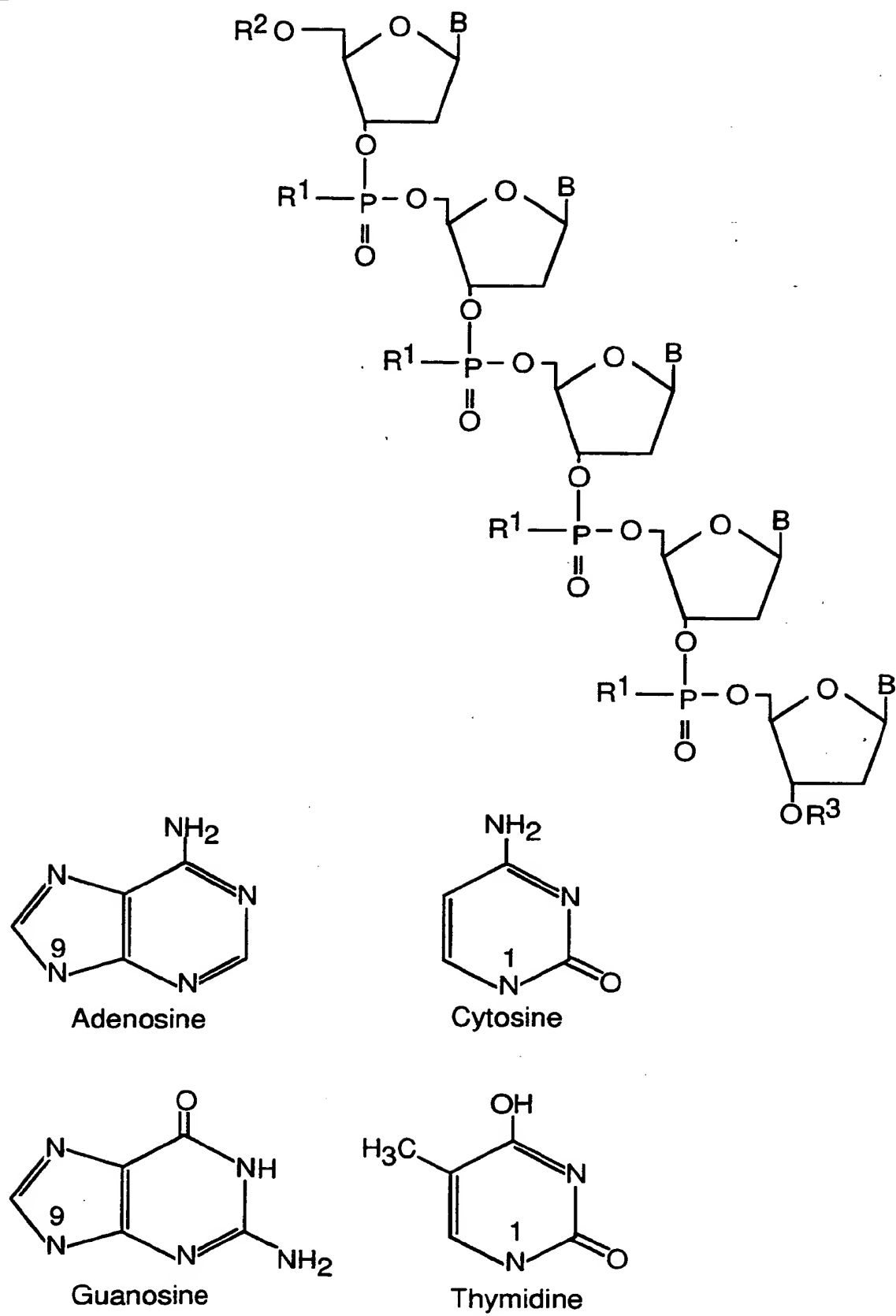
3. The pharmaceutical composition of claims 1 and/or 2, wherein the oligonucleotides are modified oligonucleotides such as phosphorothioate derivatives.
4. Antisense oligonucleotides of the pharmaceutical composition according to claim 3 and 4 as intermediate products for manufacturing the pharmaceutical composition of claims 2 and/or 3.
5. Antisense nucleic acid or -oligonucleotides according to any one of the claims 2 to 4 obtainable by solid phase synthesis using phosphite triester chemistry by growing the nucleotide chain in 3'-5' direction in that the respective nucleotide is coupled to the first nucleotide which is covalently attached to the solid phase comprising the steps of
 - cleaving 5'DMT protecting group of the previous nucleotide,
 - adding the respective nucleotide for chain propagation,
 - modifying phosphite groups subsequently cap unreacted 5'-hydroxyl groups and
 - cleaving the oligonucleotide from the solid support,
 - followed by working up the synthesis product.
6. Use of a compound according to any one of the claims 1 to 5 for the preparation of a pharmaceutical composition for the treatment of neoplasms and/or the prevention and treatment of neuronal injury and degeneration related with the expression of c-jun, c-fos or jun-B.

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7. Method of treating of neoplasms and/or preventing and treating of neuronal injury and/or degeneration by administering an effective amount of the pharmaceutical composition or the compound according to any one of the claims 1 to 5 to a patient suffering from disorders related with the expression of c-jun, c-fos or jun-B.
8. A diagnostic agent comprising a compound of the claims 1 to 5.

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Fig. 1



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Fig. 2

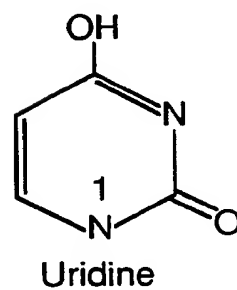
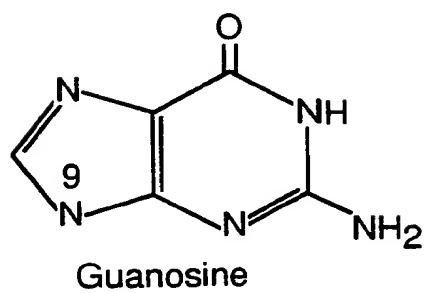
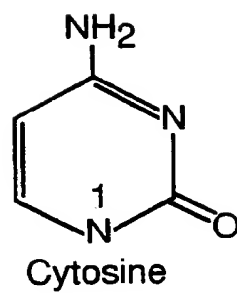
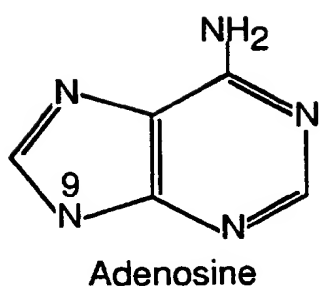
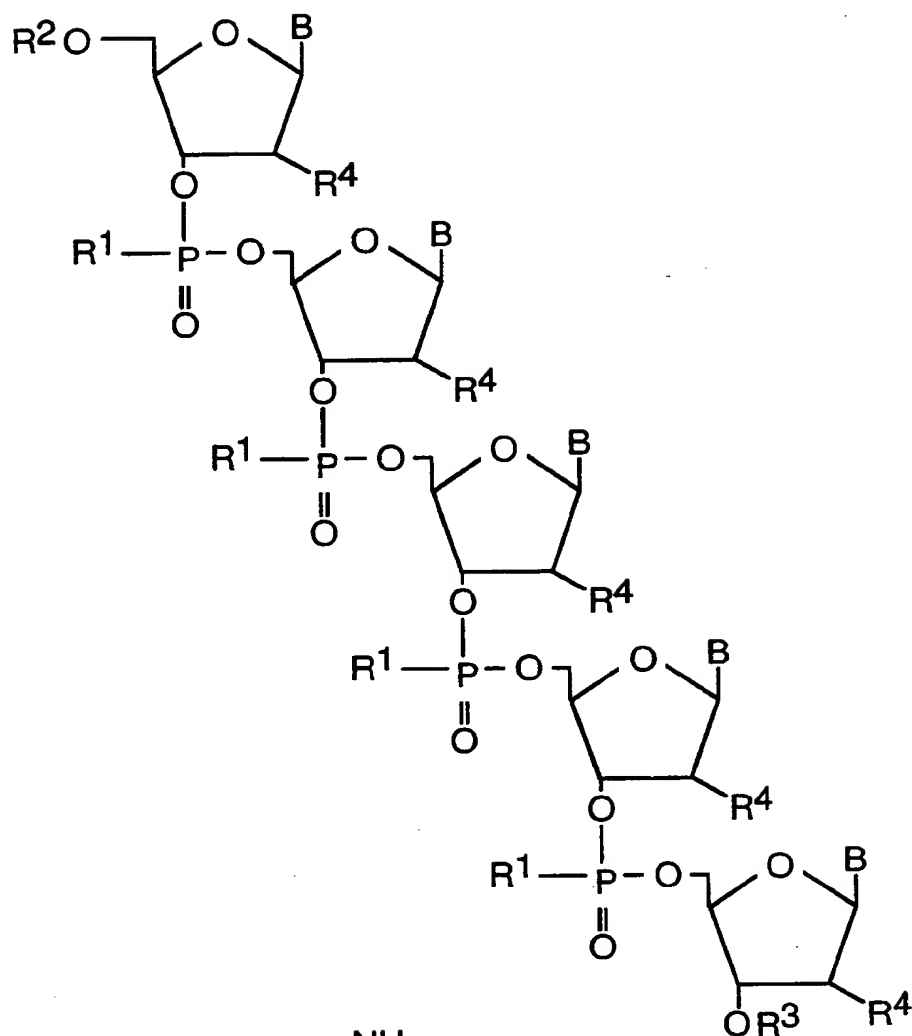


Fig. 3

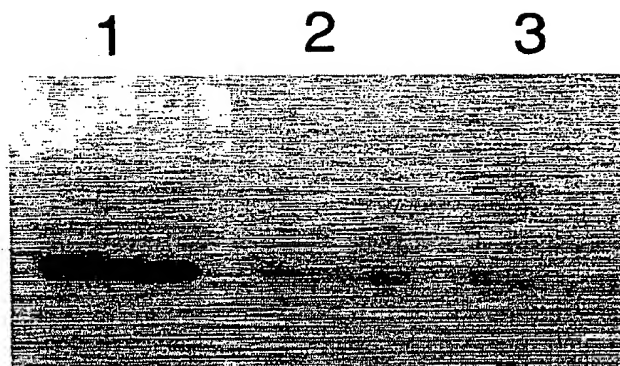
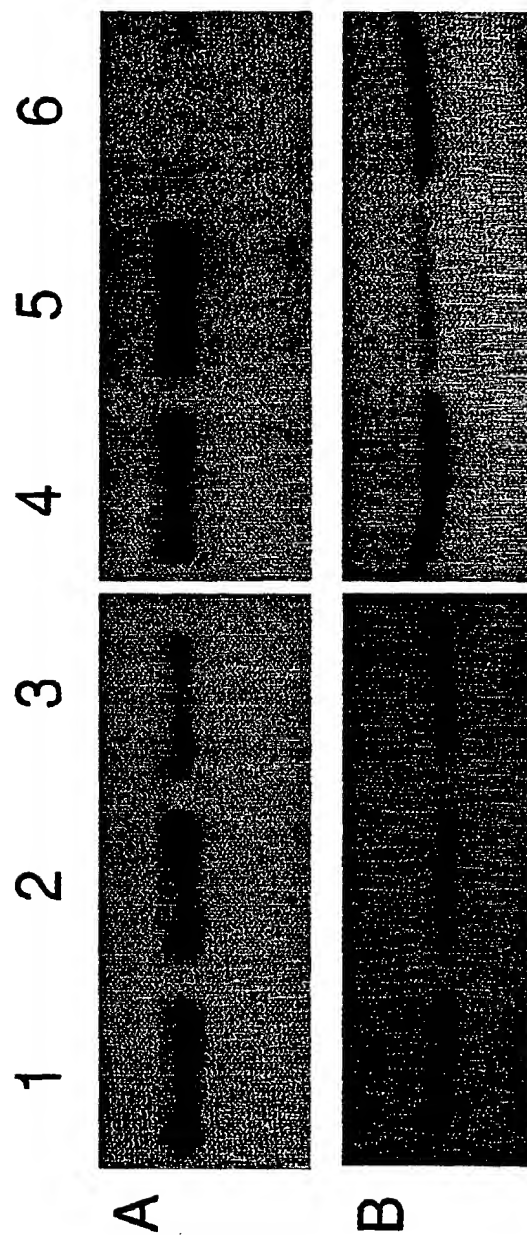


Fig. 4



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Fig. 5A Inhibition of rat c-Jun protein expression

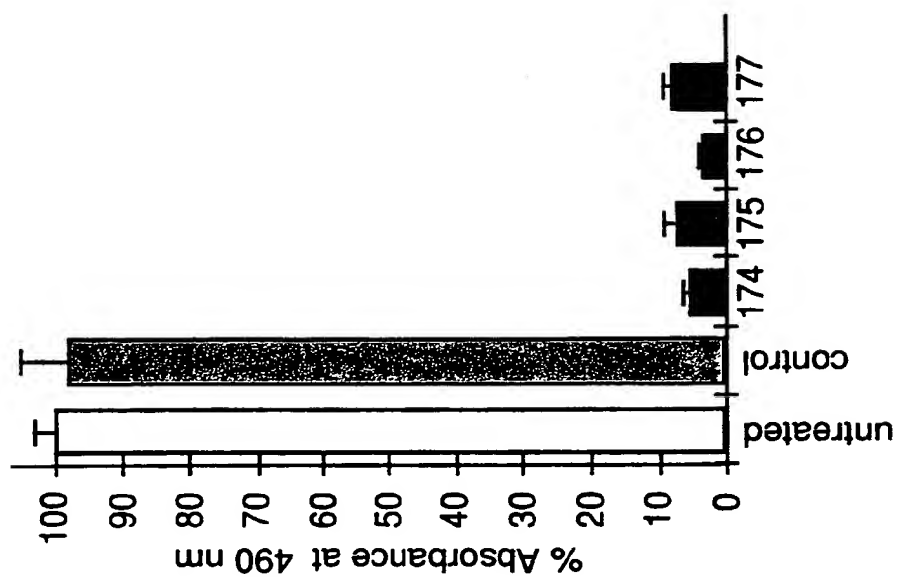


Fig. 5B Inhibition of human c-Jun protein expression

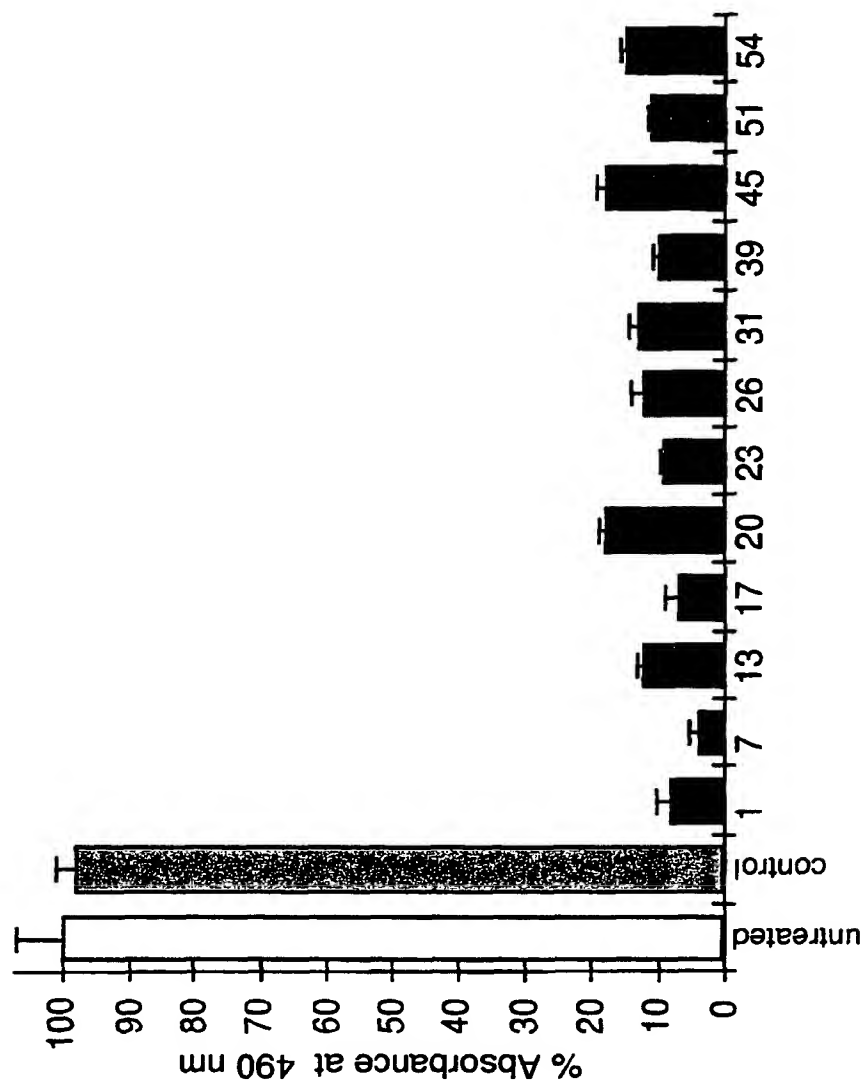


Fig. 5C Inhibition of rat Jun-B protein expression

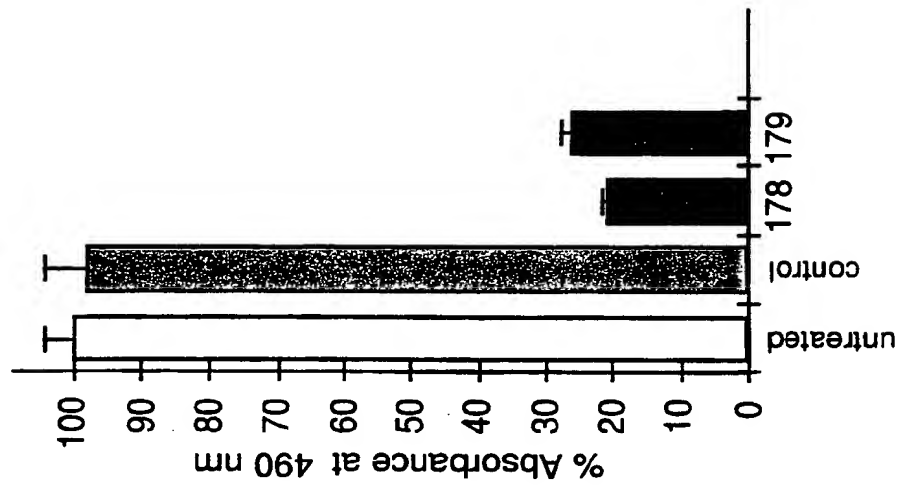
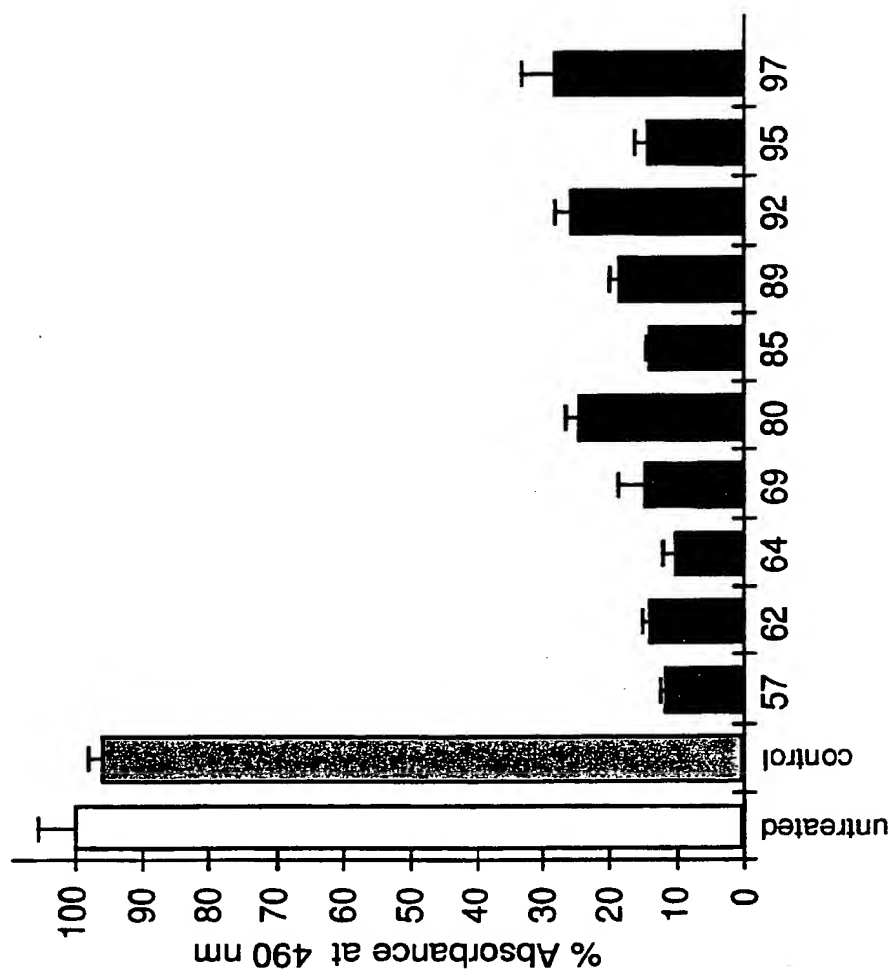


Fig. 5D Inhibition of human Jun-B protein expression



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Fig. 5E Inhibition of rat c-Fos protein expression

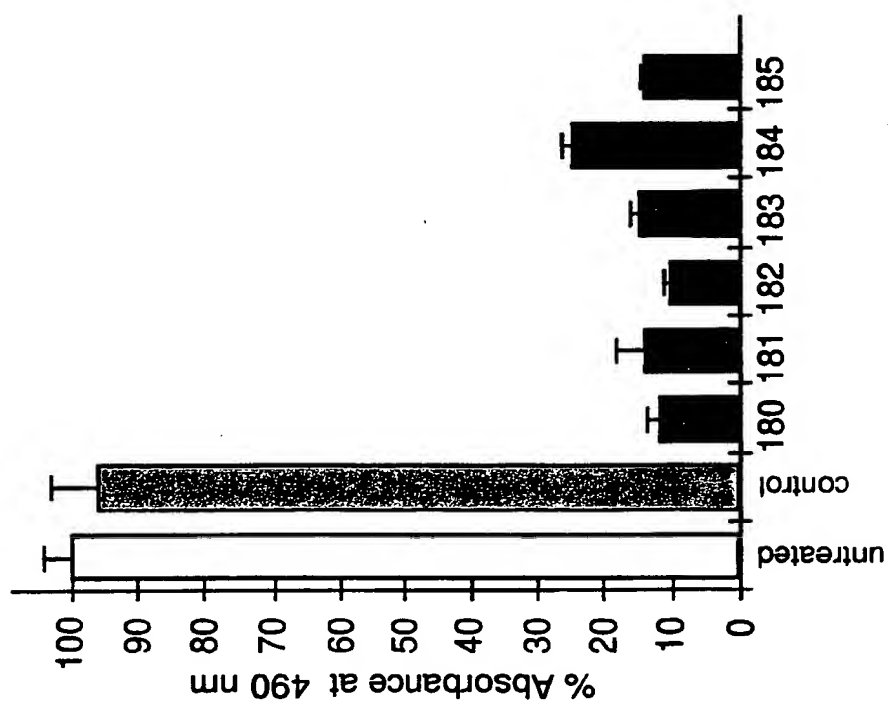
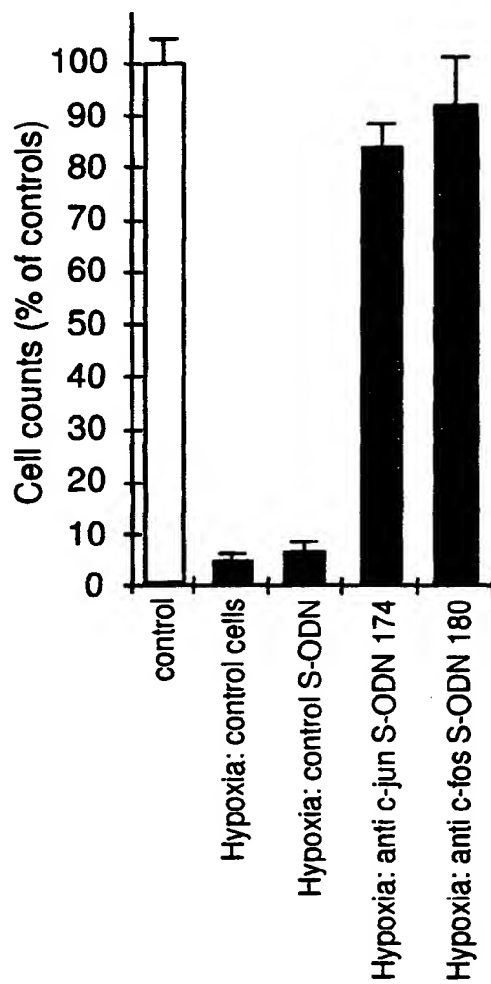


Fig. 5F Inhibition of human c-Fos protein expression



Fig. 6 Neuronal Survival



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Fig. 7 Cell number of PC-12 tumor-cells
after induction of differentiation

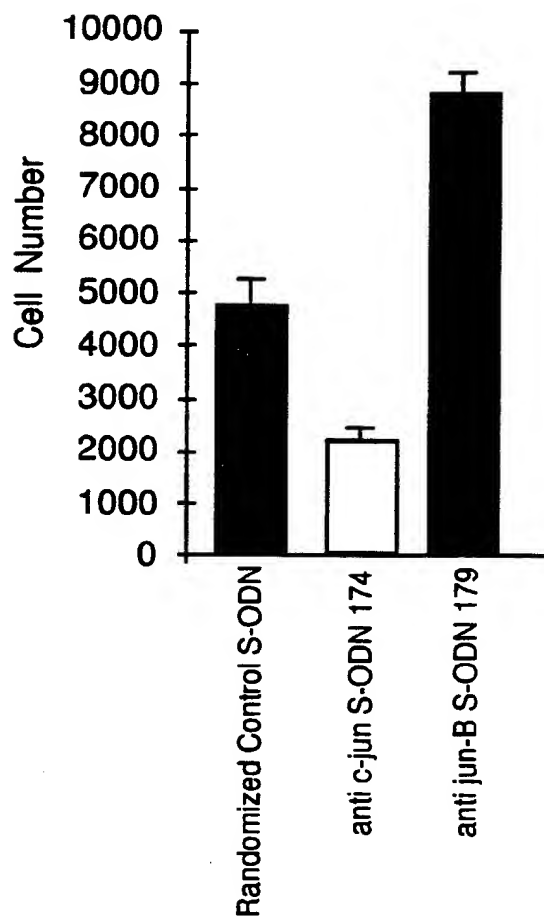
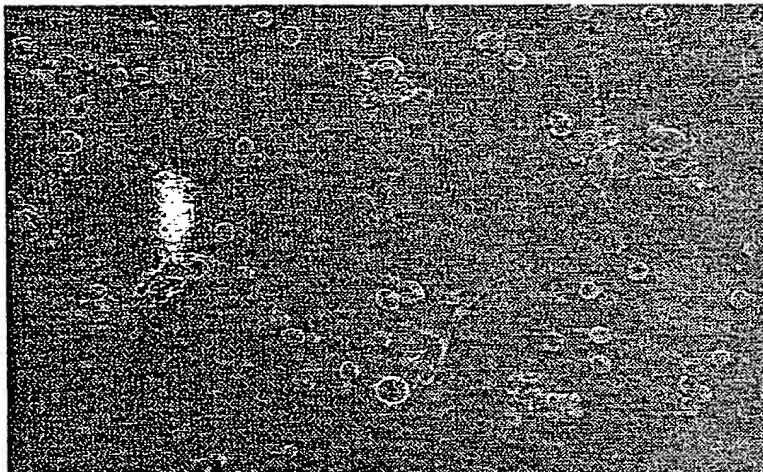
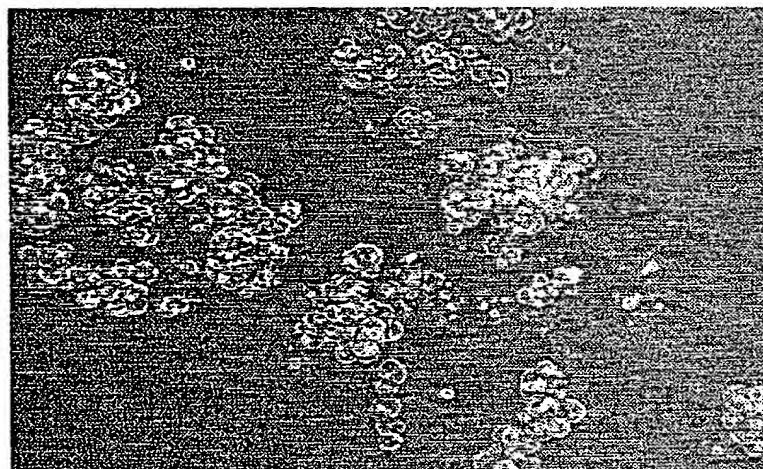
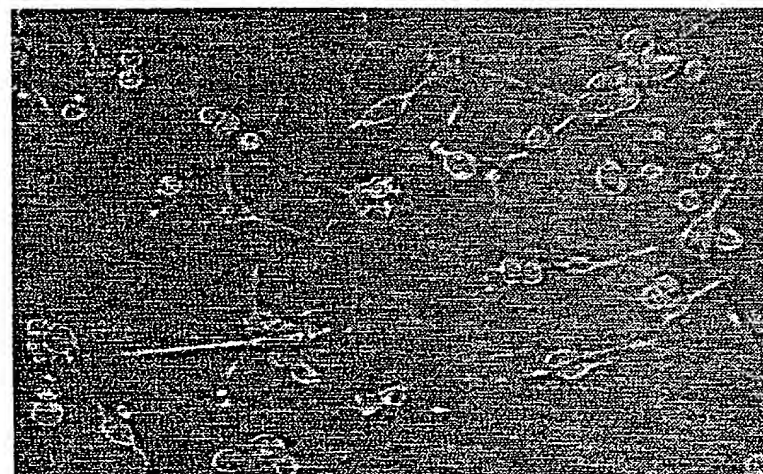


Fig. 8**A****B****C**

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(21) International Application Number: PCT/EP94/02218 (22) International Filing Date: 6 July 1994 (06.07.94) (30) Priority Data: 93111059.7 10 July 1993 (10.07.93) EP (34) Countries for which the regional or international application was filed: DE et al. (71) Applicant (for all designated States except US): BIOGNOSTIK GESELLSCHAFT FÜR BIOMOLEKULARE DIAGNOSTIK MBH [DE/DE]; Carl-Giesecke-Strasse 3, D-37079 Göttingen (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): SCHLINGENSIEPEN, Georg-F. [DE/DE]; Am Goldgraben 20, D-37073 Göttingen (DE). SCHLINGENSIEPEN, Reimar [DE/DE]; Am Goldgraben 13, D-37073 Göttingen (DE). SCHLINGENSIEPEN, Karl-Hermann [DE/DE]; Bovender Strasse 5, D-37120 Göttingen (DE). BRYSCH, Wolfgang [DE/DE]; Am Goldgraben 20, D-37073 Göttingen (DE). (74) Agents: MEYERS, Hans-Wilhelm et al.; Bahnhofsvorplatz 1 (Deichmannhaus), D-50667 Köln (DE).		(81) Designated States: AU, CA, CN, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 16 March 1995 (16.03.95)
(54) Title: A PHARMACEUTICAL COMPOSITION COMPRISING ANTISENSE-NUCLEIC ACID FOR PREVENTION AND/OR TREATMENT OF NEURONAL INJURY, DEGENERATION AND CELL DEATH AND FOR THE TREATMENT OF NEOPLASMS		
(57) Abstract A pharmaceutical composition comprising an effective amount of a compound which is capable of preventing and treating neuronal injury, degeneration, cell death and/or neoplasms in which expression of <i>c-jun</i> , <i>c-fos</i> or <i>jun-B</i> plays a causal role which compound being an antisense nucleic acid or effective derivative thereof, said antisense nucleic acid hybridizing with an area of the messenger RNA (mRNA) and/or DNA encoding <i>c-jun</i> , <i>c-fos</i> or <i>jun-B</i> .		

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